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POSITION PAPER

Integration of imaging and circulating biomarkers in heart failure: a consensus document by the Biomarkers and Imaging Study Groups of the Heart Failure Association of the European Society of Cardiology

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Circulating biomarkers and imaging techniques provide independent and complementary information to guide management of heart failure (HF). This consensus document by the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) presents current evidence-based indications relevant to integration of imaging techniques and biomarkers in HF. The document first focuses on application of circulating biomarkers together with imaging findings, in the broad domains of screening, diagnosis, risk stratification, guidance of treatment and monitoring, and then discusses specific challenging settings. In each section we crystallize clinically relevant recommendations and identify directions for future research. The target readership of this document includes cardiologists, internal medicine specialists and other clinicians dealing with HF patients.

Keywords Biomarkers • Imaging • Diagnosis • Management • Heart failure • Consensus document

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Introduction

Heart failure (HF) remains an important cause of morbidity and mortality worldwide, mandating ongoing efforts to optimize its management.[1] The screening, diagnosis, risk stratification and treatment of HF are all informed by imaging findings and levels of circulating biomarkers, especially transthoracic echocardiogram (TTE) and natriuretic peptides (NPs). The combination of imaging and laboratory findings of biomarkers has been proposed, most notably in the case of the diagnosis of HF with preserved ejection fraction (HFpEF).[2] Imaging and biomarkers have been most often considered separately, without searching for accurate and cost-effective ways to integrate the information derived from both into global algorithms that can be used in clinical practice.

The term 'biomarker' (from 'biological marker') was coined in 1989 to identify a 'measurable and quantifiable biological parameter used to assess the health and physiology of patients in terms of disease risk and diagnosis'.[3] While imaging findings could be named as biomarkers, this term is most commonly used to define circulating molecules that convey information on disease processes. At present, no position paper deals specifically with the integration of biomarkers and imaging in HF: this consensus document by the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) presents current evidence base for the integrated use of imaging techniques and biomarkers in HF. The document first covers broad applications of imaging and biomarkers (i.e. population screening, diagnosis, outcome prediction, guidance of therapy and follow-up), and then discusses specific challenging settings. In each section, clinically relevant recommendations are produced, and possible directions for future research are identified. The target readership of this document includes cardiologists, internal medicine specialists and all the physicians dealing with HF patients.

Screening

In studies incorporating systematic screening of the general population, several imaging findings were associated with HF development, most notably left ventricular (LV) systolic dysfunction and dilatation,[4,5] but also diastolic dysfunction[5,6] and LV hypertrophy.[7,8] In addition, a few studies have highlighted the prognostic value of abnormal LV deformation on speckle-tracking TTE or cardiac magnetic resonance (CMR) strain analysis in asymptomatic subjects.[9,10] Elevated B-type NP (BNP) or N-terminal pro-BNP (NT-proBNP) may be present in asymptomatic individuals with structural heart disease, who have a high risk of progressing to clinical HF.[11–16] High-sensitivity (hs) troponin I and T have very low coefficients of intra-individual variability (around 9% for hs-troponin I measured with the Architect method),[17] which is lower than NPs (e.g. 36% for NT-proBNP).[18] Therefore, even small increases in hs-troponin on repeated measurements may signal worsening cardiac damage and predict higher risk of future HF.[19,20]

The 2016 ESC position paper on cancer treatments recommended a systematic assessment using a combination of echocardiography and biomarkers in all patients before, during and after cardiotoxic cancer therapies.[21] Conversely, ESC guidelines on hypertension recommend an echocardiographic evaluation in specific cases, namely in the presence of 'ECG abnormalities or signs or symptoms of LV dysfunction' [class I, level of evidence (LOE) B], and optionally 'when the detection of LV hypertrophy may influence treatment decisions' (class IIb, LOE B).[22] The 2019 ESC guidelines on diabetes just state that 'routine assessment of circulating biomarkers is not recommended for cardiovascular risk stratification' (class III, LOE B), without any specific recommendations on echocardiography.[23] Furthermore, an ESC position paper states that 'NP measurement by general practitioners and diabetologists in high-risk populations such as those with hypertension or diabetes mellitus helps the targeted initiation of preventive measures, including medicine up-titration of renin–angiotensin system antagonists and, therefore, prevent or slow the development of HF'.[24]

A possible perspective for future research is to identify the optimal (i.e. most cost-effective) strategies to identify subclinical HF among subjects with predisposing conditions, most notably hypertension and diabetes. An integrated approach to screening might prove valuable. The finding of elevated biomarkers [BNP >50 ng/L,[25] NT-proBNP >125 ng/L,[20] or hs-troponin > upper reference limit (URL)] or increasing levels across repeated measurements (including small elevations in hs-troponin) warrants further evaluation that frequently includes performing TTE. A point-of-care TTE screening might be considered as an alternative to a two-step screening (biomarkers and then TTE) when plasma biomarker results are less accessible. Evidence of structural heart disease (such as LV dilatation and systolic dysfunction) may prompt commencing cardiac protective therapies to delay the onset of symptomatic HF (*Figure 1*). More subtle abnormalities, such as impaired global longitudinal strain (GLS),[22] may suggest intensified surveillance or the initiation of cardiac protective medications. The need for advanced imaging techniques, including CMR, should be decided on a case-by-case basis following a TTE examination.

Key point

Systematic screening for HF in the general population is likely not to be cost-effective. Screening might be considered in patients with conditions predisposing to HF, such as hypertension and diabetes, to identify subclinical HF that warrants initiation of cardiac protective therapies. A possible alternative to the current approach to HF screening in hypertensive and diabetic individuals is a two-step screening with the measurement of NPs or hs-troponin and then TTE, when circulating biomarkers are either elevated or rising. This combined approach should be evaluated in dedicated studies.

Diagnosis

The use of NPs to diagnose acute HF is well-established and recommended by major guidelines.[2,26,27] The diagnosis of non-acute HF, particularly in patients with preserved ejection fraction (HFpEF) or mildly reduced ejection fraction (HFmrEF), is more challenging.

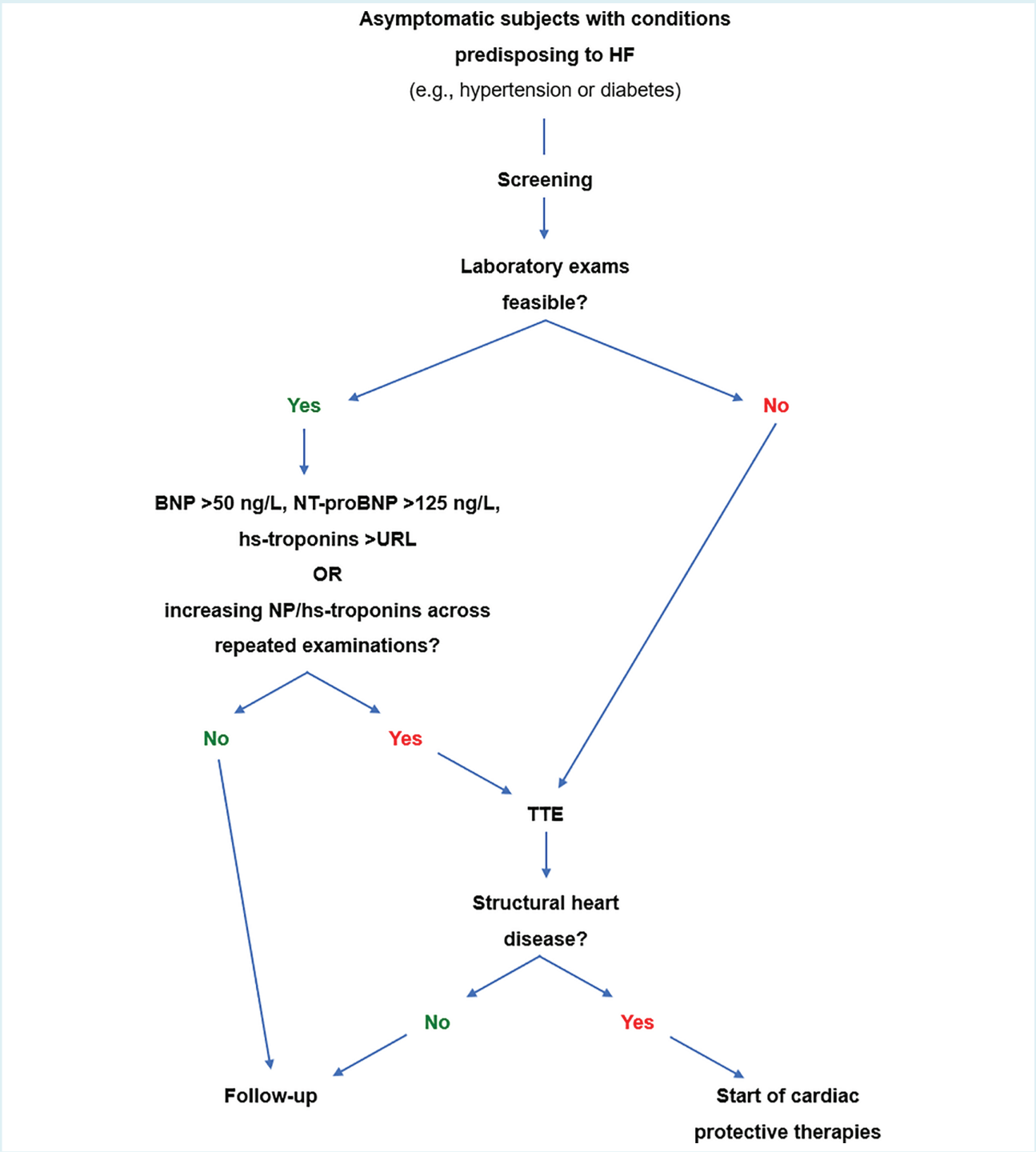

Figure 1 Proposed algorithm to screen for individuals at risk for heart failure (HF). See text for details. BNP, B-type natriuretic peptide; NP, natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TTE, transthoracic echocardiogram; URL, upper reference limit.

Heart failure with preserved ejection fraction

The diagnosis of HFpEF is a perfect example of integration between imaging and biomarkers. The 2016 ESC guidelines defined HFpEF as the combination of symptoms and/or signs of HF, LV ejection fraction (LVEF) ≥50%, elevated NP levels (BNP >35 ng/L and/or NT-proBNP >125 ng/L) together with evidence of structural heart disease [LV hypertrophy and/or left atrial (LA) enlargement] or diastolic dysfunction[2] (online supplementary *Table S1*). Indeed, the

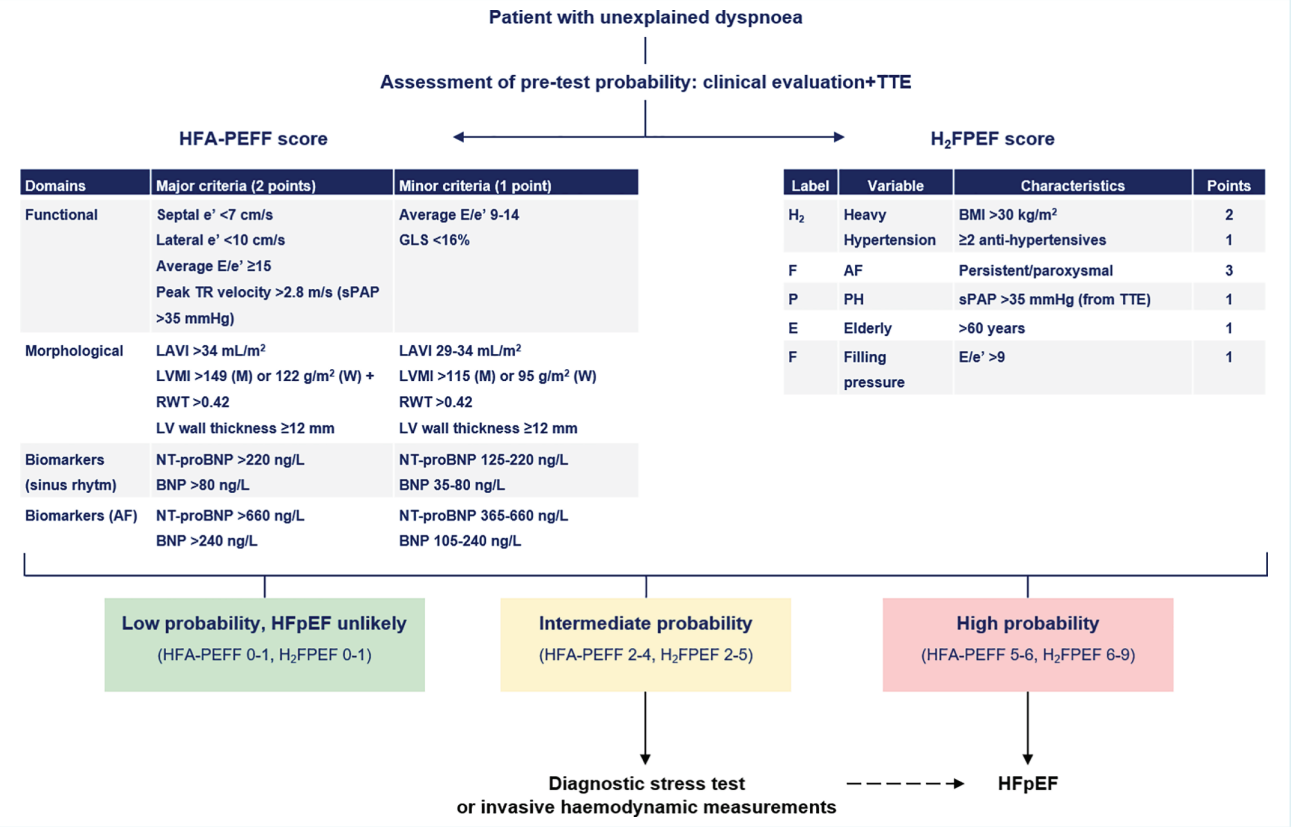

Figure 2 The HFA-PEFF and H_2FPEF scores. AF, atrial fibrillation; BMI, body mass index; BNP, B-type natriuretic peptide; GLS, global longitudinal strain; HFpEF, heart failure with preserved ejection fraction; LAVI, left atrial volume index; LV, left ventricular; LVMI, left ventricular mass index; M, men; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PH, pulmonary hypertension; RWT, relative wall thickness; sPAP, systolic pulmonary artery pressure; TR, tricuspid regurgitation; TTE, transthoracic echocardiogram; W, women.

2021 ESC guidelines defined HFpEF as the condition characterized by HF symptoms and/or signs, LVEF ≥50% and 'objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressure, including raised NPs'[28].

Overt congestion is often readily detectable from physical examination and chest X-ray, and can be corroborated by high NP levels. The diagnosis of HFpEF is more challenging in outpatients with early-stage HF who may complain of dyspnoea on effort, but do not display overt congestion.[29,30] Patients with HFpEF have lower plasma NPs than those with HF and reduced ejection fraction (HFrEF) for the same degree of congestion,[31] but differential cut-off levels of plasma NPs for HFpEF and HFrEF have not been found. Importantly, NP levels may be influenced by many cardiac and non-cardiac factors[31–33] (online supplementary *Table S2*), and should be interpreted accordingly.[24] Other biomarkers have not been systematically evaluated for their role in HFpEF diagnosis.

Right heart catheterization with measurement of pulmonary capillary wedge pressure at rest or during exercise is the gold standard for the diagnosis of HFpEF in patients with exertional dyspnoea of unclear aetiology. Costs, risks of complications, and requirements for specialized training and equipment limit its broad application. A diagnostic approach relying uniquely on exercise echocardiography is also limited.[30] The search for non-invasive alternatives to diagnose HFpEF has led to the introduction of the stepwise diagnostic algorithm HFA-PEFF,[34] the H_2FPEF score (using dichotomized variables)[35] and a HFpEF nomogram (using continuous variables)[36] (*Figure 2*).

The HFA-PEFF algorithm includes first an evaluation of risk factors and exercise intolerance. The likelihood of HFpEF is then estimated based on three domains (functional, morphological and biomarkers). A high HFA-PEFF score (5–6) allows diagnosis of HFpEF with 93% specificity, and a low HFA-PEFF score (0–1) rules out HFpEF with 99% sensitivity. Patients with an intermediate score (2–4) require further evaluation with exercise echocardiography or invasive measurement of cardiac filling pressures.[34,35,37]

The H_2FPEF score includes obesity, hypertension, atrial fibrillation (AF), pulmonary hypertension, age > 60 years and increased filling pressures. The likelihood of HFpEF is classified as low (scores 0–1), intermediate (2–5) or high (6–9), and score values are interpreted as in the case of the HFA-PEFF score.[35] Notably, the HFA-PEFF score includes NPs while the H_2FPEF score and the HFpEF nomogram do not. Head-to-head comparisons of

the two diagnostic scores are warranted to examine the added value of NP assessment beyond assessment of filling pressure by the E/e′ ratio. Another focus for future studies is integration of LA strain into the diagnostic algorithm of HFpEF. LA reservoir strain showed higher area under the curve for discrimination of HFpEF compared to E/e′ ratio, e′ velocity, LV GLS, concentric remodelling, LV hypertrophy, elevated tricuspid regurgitation (TR) velocity or indexed LA minimal volume. Therefore, LA reservoir strain may provide enhanced diagnostic accuracy beyond conventional echocardiographic measures to discriminate HFpEF from non-cardiogenic dyspnoea.[38] The added value of LA reservoir strain over NPs or other biomarkers of congestion remains to be established.

Heart failure with mildly reduced ejection fraction

The 2016 ESC HF guidelines gave separate consideration to diagnosis of HF with mid-range ejection fraction, which required symptoms and/or signs of HF, LVEF 40–49%, elevated NP levels (BNP >35 ng/L and/or NT-proBNP >125 ng/L) and at least one additional criterion: relevant structural heart disease (LV hypertrophy and/or LA enlargement) or diastolic dysfunction.[2] The recent Universal Definition of HF modified the name of HF with mid-range ejection fraction to become HF with mildly reduced ejection fraction, and introduced novel diagnostic criteria for HFmrEF, which include: (i) symptoms and/or signs caused by a structural and/or functional cardiac abnormality, (ii) elevated NP levels and/or objective evidence of pulmonary or systemic congestion, and (iii) LVEF values 41–49%.[39] Therefore, raised NPs are not mandatory where there are signs of congestion. The 2021 HF guidelines reflect this new approach and allow diagnosis of HFmrEF when symptoms and/or signs of HF are coupled with a LVEF of 41–49%.[28] Similarly, HFrEF is diagnosed when there are symptoms and signs of HF plus a LVEF ≤40%.[28]

Key point

The HFA-PEFF and H_2FPEF scores can standardize the diagnosis of HFpEF. The HFA-PEFF score includes the evaluation of NPs, but its relative diagnostic performance compared with the simpler H_2FPEF score is unclear. Diagnostic criteria for HFpEF require an integration of imaging and circulating biomarkers, while HFmrEF can be diagnosed even without evaluating NPs.

Risk prediction

Many imaging findings, including LV systolic and diastolic dysfunction,[40,41] the presence and extent of late gadolinium enhancement by CMR,[42] pulmonary hypertension and impaired right ventricular (RV) function,[43] have been associated with worse outcomes in patients with chronic HF. Circulating levels of NPs, hs-troponin and soluble suppression of tumorigenesis-2 (sST2) reflect different disease pathways and consistently improve risk prediction beyond the most extensively investigated imaging parameter, namely echocardiographic LVEF.[44,45]

Natriuretic peptides

More than 1000 studies have evaluated single and/or repeated measurements of NPs for prediction of outcomes in patients with acute or chronic HF, consistently showing high prognostic accuracy, additive to imaging findings.[24,46,47] A 2019 ESC position paper stressed the importance of NP measurement for outcome prediction in HF outpatients, but it did not provide any recommendation on risk prediction in patients with acute HF.[24]

Future development of the integrated use of NPs and imaging in chronic HF should include identification of different NP cut-offs across the spectrum of LVEF, and stratification of patients according to key confounding variables including age, sex, renal function, body mass index (BMI) and/or the presence of AF.

In acute HF, higher levels of NT-proBNP at discharge, or an inadequate decline of their levels during hospitalization, confer higher risk of readmission and/or death within 180 days. Notably, the prognostic model did not include any imaging parameter.[48] The prognostic value of admission and discharge NPs and their changes from admission to discharge should be further investigated across categories of LVEF.

High-sensitivity troponins

Increased circulating levels of hs-troponin I and T can be found in HF even in the absence of myocardial ischaemia or coronary artery disease,[49] reflecting the intensity of the ongoing cardiomyocyte damage.[50] Elevated troponin is associated with worse clinical outcomes and/or mortality irrespective of LVEF.[44,51–57] Significant and persistent falls in troponin with treatment confer a better prognosis compared to no fall or a transient decrease.[52,54–58] The 2013 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guideline recommends troponin measurement for risk stratification in acute or chronic HF (class I, LOE A)[27] while the 2016 ESC guideline does not.[2] Hs-troponin T improved risk prediction over LVEF in a cohort of 9289 patients, mostly (85%) with HFrEF. The best cut-off for the prediction of all-cause mortality, cardiovascular mortality and hospitalization for cardiovascular causes was 18 ng/L. The latter maintained prognostic significance independent of the effects of age, sex, the presence of ischaemic aetiology, LVEF, estimated glomerular filtration rate (eGFR), and NT-proBNP.[44]

The 2016 ESC HF guidelines recommend hs-troponin measurement on admission in patients with suspected acute HF within a laboratory analysis panel including full blood count, electrolytes, renal function, blood glucose, thyroid and liver function tests (class I, LOE C), with the main goal of excluding an acute coronary syndrome.[2] Conversely, the ACC/AHA guidelines recommend measuring hs-troponin T/I on admission for the purpose of risk stratification (class I, LOE A).[26] The possible integration between hs-troponin measurement and imaging is not considered in either guideline.

Soluble suppression of tumorigenesis-2

Soluble ST2 is the circulating form of the interleukin-33 membrane receptor released in response to vascular congestion,

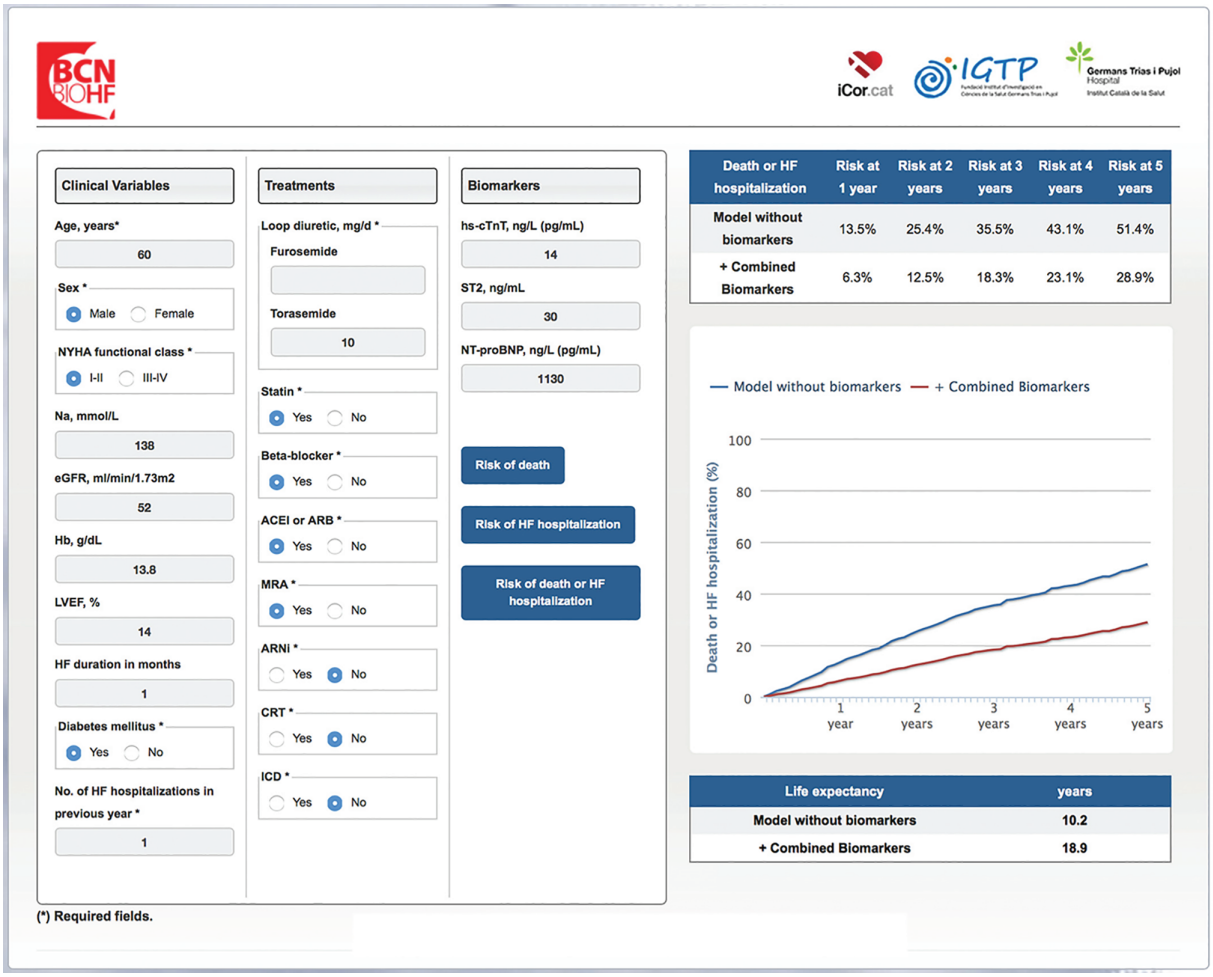

Figure 3 The Barcelona Bio-HF Calculator Version 2.0. This score provides risk estimates for 1-, 2-, 3-, 4- and 5-year mortality, heart failure (HF)-related hospitalization, and the composite endpoint for an individual patient. On the graph, the blue line represents the estimation without biomarkers (clinical model) and the red line represents the estimation with the addition of biomarkers. Reproduced from Lupón *et al.*[62]

inflammatory and pro-fibrotic stimuli.[57,58] sST2 levels are unaffected by age, sex, renal function or HFrEF/HFpEF status.[59,60] However, it can be altered by many inflammatory comorbidities,[59] which underlies its lack of utility as a diagnostic biomarker. An automated turbidimetric immunoassay for ST2 has recently been developed and validated, which may prompt increased adoption of sST2 in clinical practice.[61]

Despite these limitations, sST2 is a strong predictor of outcome in HF, the most commonly used cut-off being 35 ng/mL, predicting mortality and hospitalization in acute or chronic HF regardless of NT-proBNP, hs-troponin T, and LVEF.[45,59] The Barcelona Bio-HF Calculator Version 2.0 incorporates LVEF and other clinical variables, HF therapies (including sacubitril/valsartan) and biomarkers (sST2, NT-proBNP and hs-troponin T as continuous levels) (*Figure 3*). This score predicts all-cause mortality, HF-related hospitalization and the composite of both endpoints for up to 5 years. Biomarkers values are not mandatory for calculating this score, though their addition improves model performance. The score has been externally validated for up to 2 years.[62,63] Finally, the ST2-R2 score estimates the likelihood of reverse remodelling in HFrEF, and includes sST2 <48 ng/mL, together with baseline LVEF <24% and other variables.[64] Of note, ST2, as opposed to NPs, is weakly influenced by obesity, advanced age and chronic kidney disease (CKD).

Key point

Natriuretic peptides are established predictors of outcome in acute and chronic HF. Measurement of an hs-troponin, on at least one occasion, should be considered in outpatients with HFrEF. Patients with hs-troponin T ≥18 ng/L have a greater risk of all-cause and cardiovascular mortality and hospitalization for cardiovascular causes regardless of LVEF, NT-proBNP, age, sex, renal function and ischaemic aetiology. sST2 levels further refine risk prediction of outpatients with HFrEF with 35 ng/mL as a useful cut-off. The clinical impact and therapeutic consequences of assessing risk, however, need to be investigated in clinical trials.

Guide to treatment and follow-up

Imaging and biomarkers complement clinical history and physical examination and help guide therapy within an episode of HF decompensation and during follow-up.

Assessment of congestion

Patients with HF often develop congestion that may require urgent hospitalization, especially if lung congestion is present. Development of congestion leading to HF decompensation is a powerful predictor of poor patient outcome.[65,66] Therefore, we need to detect and monitor congestion before progression to decompensation. Congestion can be difficult to assess, especially when extrapulmonary signs of congestion are mild.[67] Increased intracardiac filling pressures often silently precede the appearance of congestive symptoms by days or weeks and mild congestion is not readily detected through bedside physical examination.[67] A history of progressive increase in body weight, dyspnoea, orthopnoea, systemic oedema, increased jugular venous pressure, and pathological third heart sound (after the age of 25 years) are all important clinical clues to congestion. However, these are often detected only once decompensation has become established.[67]

B-lines are observed on lung ultrasonography and are non-specific signs of interstitial oedema. Two small trials showed the potential of B-lines as a treatment target in chronic HF (<3 B-lines in eight thoracic sites).[68,69] A higher threshold (≥3 B-lines in at least two windows bilaterally) was suggested in acute HF.[70,71] Other aetiologies for B-lines, such as pulmonary fibrosis, should be excluded. Circulating biomarkers (most notably elevated NPs) improve the specificity of B-lines on lung ultrasonography.

The role of echocardiography in assessing congestion was specifically analysed in a previous position paper from the ESC.[72] Briefly, echocardiography allows a point-of-care assessment of LV filling pattern and pulmonary artery pressure. An E/e′ ratio ≥15 denotes increased LV diastolic pressure consistent with HF decompensation,[73] and effective decongestion results in a rapid decrease in E/e′.[74] In a small trial, a therapeutic strategy relying on lung and inferior vena cava ultrasound and on E/e′ measurement resulted in greater decongestion during shorter hospitalization without increased adverse events, compared to standard care, although the therapeutic workup was not standardized based on echocardiographic findings.[75]

Haemoconcentration, as assessed by increasing haemoglobin, haematocrit, albumin and total protein during decongestion, is predictive of outcome,[75] but there are no reliable cut-offs to differentiate euvolaemic from congested patients. Early haemoconcentration offers little prognostic information, as rapid intravascular refilling from the interstitial compartment can counterbalance the initial response to decongestive therapies.[76,77] Creatinine, often used as a biomarker to adjust diuretic therapy, is not reliable as it may rise in both hyper- and hypovolaemia.[78] Importantly, a rising creatinine in the setting of successful decongestion may predict a better outcome,[79] nevertheless its rise should prompt a re-evaluation of fluid status. Effective decongestion is also accompanied by decreasing NPs, with some reports of a better survival of patients with a more pronounced decrease.[80] Furthermore, sST2 acts as a biomarker of congestion, and percent changes in sST2 are predictive of 90-day mortality regardless of NP levels.[81] At present, we lack sufficient evidence to define plasma thresholds to trigger further clinical assessment or adjustment of therapy.

An algorithm for congestion management integrating imaging and biomarkers is shown in *Figure 4*. It incorporates signs and symptoms and the dynamics of blood biomarkers, including NPs, creatinine and full blood count. Asymptomatic patients with low NPs and no unfavourable changes in NPs, creatinine and haemoglobin/haematocrit should be followed routinely. Symptomatic patients or those with blood biomarkers suggestive of congestion should undergo sonographic volume status assessment. The selection of imaging markers of congestion depends on available time, ultrasound device availability and the experience of the echocardiographer. At least two imaging markers for congestion should be positive to trigger escalation of therapy. Prospective randomized clinical trials are needed to ascertain if interventions based on this integrated approach improve outcomes.

Key point

Circulating biomarkers play an important role as indicators for sonographic fluid status assessment and will improve the specificity of sonographic findings. We need well-designed randomized clinical trials to test the concept of echo-guided decongestion with defined cut-offs for both echocardiographic measures and adjunctive circulating markers. Meanwhile, imaging markers and concurrent circulating biomarkers should be interpreted on a case-by-case basis.

Guide to heart failure therapy and follow-up

Imaging is required for allocation of certain HF treatments and to detect complications such as adverse LV remodelling[82] and functional mitral regurgitation.[83,84] Follow-up examinations are typically represented by serial echocardiograms; repeated CMR exams may be considered in selected cases. The latter allow accurate characterization of changes in chamber volumes and function and longitudinal assessment of tissue composition over time.

Among patients with chronic ambulatory HFrEF, reducing NT-proBNP to below 1000 ng/L within 12 months was associated with LV reverse remodelling and better outcomes.[85] Sustained reduction of NT-proBNP in HFrEF has been found to be associated with stable improvement in LV function and low likelihood of progressive remodelling.[86] A low NT-proBNP might obviate needless serial imaging in such patients.

Several meta-analyses of small-to-medium scale prospective trials have found a prognostic benefit from NP-guided therapy in HFrEF.[87–90] The Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) trial did not show a sustained difference in intensity of pharmacotherapy between study groups and no survival benefit from NT-proBNP-guided therapy. However, this trial achieved no difference in pharmacotherapy between study limbs.[91]

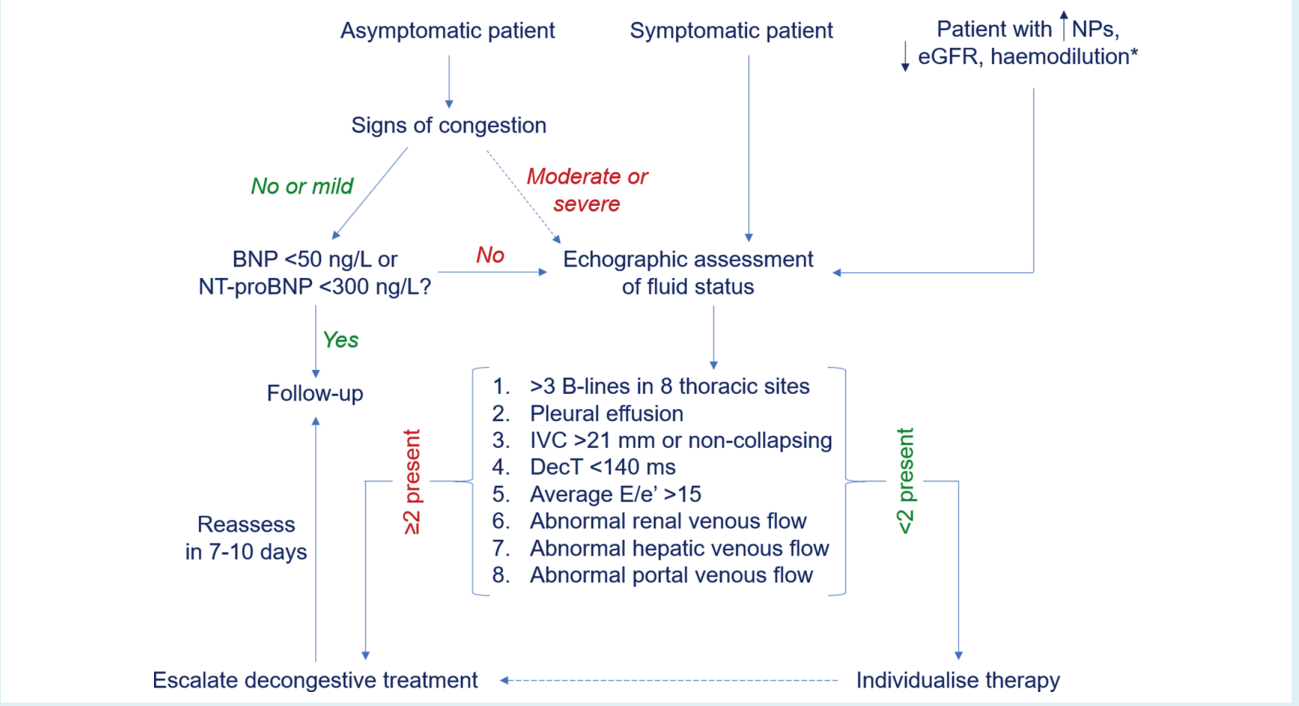

Figure 4 Proposed algorithm for integrated imaging and laboratory evaluation to guide congestion management. The dashed arrow means that asymptomatic patients are unlikely to have moderate or severe signs of congestion. BNP, B-type natriuretic peptide; DecT, E-wave deceleration time; eGFR, estimated glomerular filtration rate; IVC, inferior vena cava; NP, natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide. *Decreasing haemoglobin or haematocrit or albumin or total protein, unexplained by other reasons than progressing congestion.

Other biomarkers such as sST2, eGFR or the combination of multiple markers have been retrospectively investigated as tools to individualize therapy.[92–95] Prospective trials of marker-based guidance of treatment, including assessment of multi-marker approaches, are needed.

Key point

In chronic HFrEF, achieving concentrations of NT-proBNP <1000 ng/L is associated with LV reverse remodelling and a better prognosis. Sustained reduction in NT-proBNP below this level may allow a less intensive patient follow-up.

Heart failure with recovered/improved ejection fraction

The Universal Definition of HF has recently highlighted HF with improved ejection fraction (HFimpEF), defined as symptomatic HF with a baseline LVEF ≤40%, a ≥ 10-point increase from baseline LVEF, and a second LVEF measurement >40%.[40] This group replaces the previous entity of HF with recovered ejection fraction, which lacked a standard definition.

Left ventricular ejection fraction recovery has long been described in patients with HFrEF due to peripartum cardiomyopathy, alcohol abuse, myocarditis and ischaemic heart disease.[96–98] In recent-onset dilated cardiomyopathy, LVEF improved in 45% of patients at 12 months,[99] and in one third of cases within a 2-year follow-up when dilated cardiomyopathy was present for more than 1 year (thus excluding resolving acute myocarditis).[100] Significant improvement in LVEF has been observed in elderly patients with chronic HFrEF with intensification of therapy, regardless of the underlying cause.[96,97]

High rates of restoration of cardiac function have also been described in Takotsubo cardiomyopathy, toxic cardiomyopathy and peri-partum cardiomyopathy.[98,101] However, recovery cannot be defined solely by normalization of LVEF, as outcomes in this group remain worse than in controls (giving further support to the replacement of its old name by HFimpEF).[102] Other relevant parameters of reverse remodelling include changes in LV end-diastolic volume or GLS.[103,104] An increase in absolute GLS values >16% is predictive of sustained normalization of LVEF and good prognosis.[105]

Patients with HFimpEF may display continuing elevations of plasma NPs and troponin, denoting active haemodynamic overload and ongoing cardiomyocyte damage.[106] Although older age, discontinuation of therapy and longer HF duration are all associated with recurrence of HFrEF in HFimpEF, reliable prediction of future deterioration of cardiac function in individual patients remains challenging.[106] In a randomized study, HF therapy was withdrawn in a controlled setting in HF patients with improved LVEF, normal LV end-diastolic volume and NT-proBNP <250 ng/L (around 10% of an unselected HF cohort).[104] During and after down-titration of HF therapy, nearly half of the patients exhibited

recurrent LV abnormalities without significant symptomatic clinical events. The combination of persistently elevated NT-proBNP and reduced radial strain on CMR best predicted new deterioration of LV parameters.

Key point

Heart failure recovery is revealed by longitudinal changes in imaging findings, most commonly from repeated echocardiography, and is accompanied by a reduction in NPs. Our current state of knowledge suggests that HF medications should be continued in patients with HFimpEF to prevent a new decline of cardiac function in a large proportion of this group. Rising NT-proBNP portends new deterioration of LV function in HFimpEF.

Guide to defibrillator implantation

The indications for an implantable cardioverter defibrillator (ICD) for primary prevention currently comprise LVEF <35% and ischaemic (LOE A) or non-ischaemic (LOE B) HF.[2] However, the Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality (DANISH) trial recruited patients on modern pharmacotherapy, as per the 2012 ESC guidelines,[107] and failed to demonstrate a survival benefit of ICDs in non-ischaemic HF.[108] Thus, although risk stratification based on LVEF is practical, there is a clear need to further refine patient selection. Patients with a high burden of fibrosis (such as late gadolinium enhancement >5% of the left ventricle) are at increased risk of arrhythmic death and should be considered for ICD therapy even if their LVEF is not severely depressed.[109–111] Likewise, the absence of fibrosis is a powerful predictor of freedom from ventricular arrhythmias, possibly supporting deferred implantation. As for biomarkers related to fibrosis, several studies have linked higher sST2 levels to a higher risk of sudden cardiac death (SCD) in several settings, such as patients without an ICD but severe systolic dysfunction at baseline (mean LVEF 30%),[112] or patients with better systolic function (mean LVEF 37%), but still no ICD at baseline.[113] In the latter setting, a model including sST2 >45 ng/mL, LVEF <45%, HF duration >3 years, eGFR <55 mL/min/1.73 m^2, age ≥60 years and male sex (the ST2-SCD score) has been proposed and validated.[112,113] It is reasonable to state that raised sST2 strengthens the indication for ICD for primary prevention, although prospective tests of this strategy are required.

Key point

Raised sST2 is associated with an increased risk of SCD and supports the decision to implant an ICD for primary prevention.

Guide to cardiac resynchronization therapy

Cardiac resynchronization therapy (CRT) is currently indicated according to clinical, imaging and electrocardiographic findings. Imaging may assist decision-making on CRT implantation. On CMR, a large transmural myocardial scar predicted lack of benefit from CRT.[114] In a single small study, diffuse myocardial fibrosis assessed by T1 mapping did not correlate with response to CRT.[115]

With respect to circulating markers, an observational study found that lower pro-collagen type I C-terminal pro-peptide (PICP, a marker of myocardial fibrosis) displayed an association with response to CRT independent of other predictors such as left bundle branch block, QRS duration, non-ischaemic aetiology, or lead position.[116] However, this conflicts with a previous report that higher fibrogenesis (as assessed by the ratio of PICP to C-terminal telopeptide of type I collagen) correlated with greater response to CRT.[117] Similarly, in a sub-study of the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT), patients with the highest baseline levels of galectin-3 (a mediator of fibrogenesis) derived greater benefit from CRT with defibrillator capability.[118]

Key point

The current discrepant state of evidence does not allow any clear recommendation about the possibility to guide CRT implantation based on circulating biomarkers or imaging findings related to myocardial fibrosis. Larger data sets with longer periods of follow-up assessing a wider range of candidate markers are required.

Specific scenarios

Atrial fibrillation

Patients with AF have higher NPs at any given filling pressure.[119] Accordingly, AF reduces the performance of NT-proBNP in discriminating acute HF from other causes of new-onset dyspnoea, with an area under the curve of 0.7 vs. 0.9 in patients in sinus rhythm. The widely accepted rule-out threshold of 300 ng/L remains highly sensitive, but poorly specific (<20%).[120] Different diagnostic cut-offs have been proposed to improve specificity. The HFA-PEFF algorithm suggests an elevation of BNP >240 ng/L or NT-proBNP >660 ng/L as a major criterion for the diagnosis of HFpEF in patients with AF, compared to BNP >80 ng/L or NT-proBNP >220 ng/L in patients in sinus rhythm[35] (*Figure 1*). These cut-offs should be critically interpreted, and patients with AF suffering dyspnoea without overt congestion should be referred to exercise testing given the high probability of underlying HFpEF.[121]

The HFA-PEFF algorithm lists an LA volume index >40 mL/m^2 as a major diagnostic criterion,[35] a higher threshold than in sinus rhythm. An Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48 (ENGAGE AF-TIMI 48) echocardiographic sub-study demonstrated that two functional indices (LA emptying fraction and expansion index) are stronger predictors of cardiovascular death or HF hospitalization than LA volume index.[122] LA strain analysis might be considered in patients with HFpEF who have paroxysmal or persistent AF to predict the likelihood of progression to permanent AF.[123]

Table 1 Approximate cut-off levels of natriuretic peptides to diagnose heart failure in obese individuals

	Cut-off levels (ng/L)					
	NT-proBNP			BNP		
	<50 years	50–75 years	>75 years	<50 years	50–75 years	>75 years
Acute setting, patient with acute dyspnoea						
HF unlikely		<150			<50	
'Grey zone'	150–225	150–450	150–900		50–200	
HF likely	>225	>450	>900		>200	
Non-acute setting, patient with mild symptoms						
HF unlikely		<63			<18	
'Grey zone'		63–300			18–75	
HF likely		>300			>75	

Modified from Mueller *et al.*[24]
BNP, B-type natriuretic peptide; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Echocardiographic estimation of pulmonary artery pressure from TR velocity correlates well with invasive measurements irrespective of AF, and a peak TR velocity >2.8 m/s (corresponding to a systolic pulmonary artery pressure >35 mmHg) discriminates patients with HFpEF from those with hypertension but no HF.[124] Both E/e′ ≥15 and a peak TR velocity >3.4 m/s are used to diagnose HF during exercise echocardiography (diastolic stress test), but their use in AF is more challenging.[35]

Obesity

Obesity is a common risk factor for HF, particularly HFpEF.[125] While obese patients with HFpEF are often highly symptomatic,[126,127] correct identification of symptoms and signs of HF in obese individuals may be challenging. The transthoracic acoustic window is frequently poor in the obese and LA dilatation may be missed because of indexing issues. Furthermore, NP levels can be misleading in this population given the inverse relationship between NPs and obesity. This is maintained in the setting of HF, with lower levels of circulating NPs in obese individuals with acute and chronic HF compared to lean individuals with HF.[128–131] The inverse relationship of NPs with high BMI is present in both HFrEF and HFpEF, although median levels are higher in HFrEF. As discussed in detail in a recent review paper,[132] the need for BMI-specific cut-offs is debated, but has been endorsed by an ESC HFA position paper, which proposed the use of 50% lower NP cut-offs to diagnose acute or non-acute HF in obese individuals (*Table 1*).[24] The prognostic value of NPs in acute and chronic HF is preserved across BMI classes.[133–136]

Chronic kidney disease

Reduced eGFR has little influence on plasma NPs until it falls to <30 mL/min/1.73 m^2.[137,138] In CKD stages 4–5, particularly in patients on dialysis, NPs are markedly elevated and no established diagnostic thresholds exist. Integration between laboratory and imaging data then becomes particularly important. For example, the combination of elevated NP together with echocardiographic indicators of increased LV filling pressure (E/e′ ≥15) aid to diagnose HF in patients with new-onset dyspnoea.

Natriuretic peptide values retain a prognostic role even in patients with advanced CKD,[139] and several echocardiographic variables, including from speckle-tracking analysis, help predict patient outcome. For example, LV GLS holds greater prognostic value than LVEF in advanced CKD,[140,141] and RV GLS is a specific marker of subclinical RV dysfunction in CKD even when RV fractional area change remains normal.[142] Use of contrast-enhanced CMR is restricted to patients with eGFR ≥30 mL/min/1.73 m^2. New modalities, such as native T1 mapping, are being considered with interest.[143–145]

Overall, circulating and imaging biomarkers convey complementary diagnostic and prognostic information in patients with advanced CKD, but optimal integration remains to be defined and formally evaluated.

Right ventricular dysfunction and pulmonary hypertension

Imaging data, particularly those from TTE, define RV dysfunction and indicate pulmonary artery pressure. There are no specific plasma biomarkers for the diagnosis of RV dysfunction and pulmonary hypertension, but NPs are strongly prognostic in both.[146–148] Therefore, the integration of echocardiographic findings and NP levels refines risk stratification, as reported for the combination of tricuspid annular plane systolic excursion <15 mm and NT-proBNP ≥500 ng/L in patients with pulmonary hypertension due to congenital heart disease.[148] The roles of biomarkers other than NPs (troponin, sST2, galectin-3 and growth differentiation factor-15) and advanced imaging techniques are under investigation.[149,150]

Heart valve disease

Optimal timing of valve surgery or repair to preserve LV geometry and function and relieve HF symptoms is often challenging. The

combined assessment of biomarkers and imaging can help plan surgical or percutaneous interventions, especially when patients are asymptomatic or have unclear symptoms.

The strongest indication for valve surgery for aortic regurgitation is the presence of symptoms (either at rest or during exercise); however, even if the patient was asymptomatic, surgery is indicated in the presence of any one of the following: LVEF <50%, LV end-diastolic diameter >70 mm, LV end-systolic diameter (LVESD) >50 mm or an indexed LVESD >25 mm/m^2.[151] In severe asymptomatic aortic regurgitation with normal LV function, BNP >130 ng/L identifies a subgroup with higher risk.[152]

Natriuretic peptides predict outcomes in severe aortic stenosis (AS), including low-flow AS.[153,154] In asymptomatic severe AS, BNP <130 ng/L and NT-proBNP <592 ng/L predict a lower risk of symptom development and a lower need for surgery over the following year.[153] BNP <100 ng/L was associated with a low rate of AS-related events.[155]

In patients with asymptomatic severe mitral regurgitation (MR), LVEF <60% or LVESD >45 mm, or in their absence systolic pulmonary artery pressure >50 mmHg should prompt the referral to surgery.[151,156,157] Elevated or increasing NPs are predictive of symptom development and adverse outcome. In severe asymptomatic primary MR, BNP ≥105 ng/L predicts a higher risk of LV dysfunction, HF or death over 3 years.[158] The combination of BNP and GLS better defined risk than either variable alone in asymptomatic, significant primary MR with preserved LVEF.[159]

B-type natriuretic peptide is directly correlated with RV volume and inversely with LVEF after surgery for severe isolated TR. BNP <200 ng/L was associated with lower postoperative mortality at 1 year.[160]

Cardiac amyloidosis

In cardiac amyloidosis, misfolded proteins lead to accumulation of insoluble amyloid fibrils, composed of immunoglobulin light-chains (AL) or transthyretin (ATTR).[161,162] Both echocardiography and biomarkers are included in the first step of the diagnostic algorithm of CA. Echocardiographic features in CA include increased LV and/or RV wall thickness (often with a sparkling appearance) and diastolic dysfunction.[163] Speckle-tracking imaging is sensitive to early systolic dysfunction and typically displays preserved apical contractility.[164–166] GLS < −17%, lack of 'apical sparing' and hs-troponin T <35 ng/L help rule out cardiac involvement in systemic AL amyloidosis.[167] Risk stratification in AL- and ATTR-CA relies on biomarkers, as demonstrated by the proposed scores. Optimal integration of biomarkers and imaging remains to be defined and should be pursued in future studies.[168]

Myocarditis

Endomyocardial biopsy remains the gold standard for the diagnosis of myocarditis, but is usually reserved for cases with reduced LV function, recurrent troponin increases, or suspicion of specific aetiologies.[169] The non-invasive diagnosis of myocarditis requires CMR examination and relies on the Lake Louise criteria, which include oedema on T2-weighted imaging, hyperaemia on early gadolinium enhancement images and necrosis/oedema on late gadolinium enhancement images. Myocarditis can be diagnosed when at least two of these hallmarks of inflammation are present.[170] Troponin is usually raised in these patients, but normal concentrations do not exclude the diagnosis.[169]

Rejection after heart transplantation

Serial endomyocardial biopsies are routinely performed in the first year after heart transplantation to detect allograft rejection. Subsequently, annual non-invasive imaging is used to check for rejection.[171] Decreased LVEF is typically a late finding and does not correlate reliably with the grade of rejection found on endomyocardial biopsy.[172] The variability and low sensitivity and specificity of NPs limit their usefulness in this setting.[173]

In case of acute rejection, TTE typically reveals abnormal diastolic indices. Tissue Doppler diastolic velocities and isovolumic relaxation time are the most sensitive indicators.[174,175] RV free wall longitudinal strain <17% and LV GLS <15.5% are independent predictors of acute rejection with a negative predictive value of 100%, albeit with a low positive predictive value (<25%).[176,177] CMR can evaluate inflammation/rejection-related expansion of interstitial volume by calculation of extracellular volume. Myocardial T2 relaxation time is associated with myocardial oedema.[178] T2 mapping holds promise in acute rejection with sensitive threshold T2 values of ≥60 ms on 1.5 T CMR.[179–181] Cardiac biomarkers, including NT-proBNP and hs-troponin, have received limited attention as tools to detect or predict acute rejection.

Guideline recommendations and possible further roles of integration of imaging and circulating biomarkers

In *Table 2* we report the recommendations from ESC and ACC/AHA guidelines on the use of imaging and circulating biomarkers for screening, diagnosis, risk stratification and guiding treatment in HF, and we add the key points summarizing the contents of this paper.

With the growing number of therapeutic options for HF, an individually tailored approach is becoming increasingly important. This entails consideration of aetiology, type and severity of cardiac dysfunction, along with age, gender and comorbidities. The availability of circulating biomarkers associated with haemodynamic burden, neurohormonal activation, ongoing myocardial damage and activation of proinflammatory and profibrotic pathways can complement multi-modal imaging techniques for defining cardiac morphology and function, the progression of fibrosis and adverse or reverse remodelling. Integrating circulating markers with imaging will allow us to progressively identify patient-centred and condition-specific approaches to HF assessment and management.

Table 2 Current guidelines on biomarkers and imaging in heart failure and recommendations for their integrated use

Setting	2016 ESC HF Guideline	2017 ACC/AHA/HFSA Focused update of the 2013 ACCF/AHA HF guideline	Key points
Screening	TTE is recommended for the assessment of myocardial structure and function in subjects to be exposed to treatment which potentially can damage myocardium (e.g. chemotherapy) (class I, LOE C) Other techniques (including systolic tissue Doppler velocities and deformation indices, i.e. strain and strain rate), should be considered in a TTE protocol in subjects at risk of developing HF to identify myocardial dysfunction at the preclinical stage (class IIa, LOE C)	For patients at risk of developing HF, NP biomarker–based screening followed by team-based care, including a cardiovascular specialist optimizing GDMT, can be useful to prevent the development of LV dysfunction (systolic or diastolic) or new-onset HF	Systematic screening for HF in the general population is likely not to be cost-effective. Screening might be considered in patients with conditions predisposing to HF, such as hypertension and diabetes, to identify subclinical HF that warrants initiation of cardiac protective therapies. A possible alternative to the current approach to HF screening in hypertensive and diabetic individuals is a two-step screening with the measurement of NPs or hs-troponin and then TTE, when circulating biomarkers are either elevated or rising. This combined approach should be evaluated in dedicated studies
Diagnosis	Diagnostic criteria: elevated NP needed for HFmrEF/HFpEF diagnosis (BNP >35 ng/L and/or NT-proBNP >125 ng/L)	In ambulatory patients with dyspnoea, measurement of BNP or NT-proBNP is useful to support clinical decision-making regarding the diagnosis of HF, especially in the setting of clinical uncertainty (class I, LOE A) Measurement of BNP or NT-proBNP is useful to support clinical judgment for the diagnosis of acutely decompensated HF, especially in the setting of uncertainty for the diagnosis (class I, LOE A) Patients with suspected or new-onset HF, or those presenting with acute decompensated HF, should undergo a chest X-ray to assess heart size and pulmonary congestion and to detect alternative cardiac, pulmonary, and other diseases that may cause or contribute to the patient symptoms (class I, LOE C)	The HFA-PEFF and H_2FPEF scores can standardize the diagnosis of HFpEF. The HFA-PEFF score includes the evaluation of NPs, but its relative diagnostic performance compared with the simpler H_2FPEF score is unclear. Diagnostic criteria for HFpEF require an integration of imaging and circulating biomarkers, while HFmrEF can be diagnosed even without evaluating NPs
	TTE is recommended for the assessment of myocardial structure and function in subjects with suspected HF in order to establish a diagnosis of either HFrEF, HFmrEF or HFpEF (class I, LOE C)	A two-dimensional echocardiogram with Doppler should be performed during initial evaluation of patients presenting with HF to assess ventricular function, size, wall thickness, wall motion, and valve function (class I, LOE C)	
	CMR is recommended for the assessment of myocardial structure and function (including right heart) in subjects with poor acoustic window and patients with complex congenital heart diseases (taking account of cautions/contraindications to CMR) (class I, LOE C)	Radionuclide ventriculography or magnetic resonance imaging can be useful to assess LVEF and volume when echocardiography is inadequate (class IIa, LOE C)	

Table 2 (Continued)

Setting	2016 ESC HF Guideline	2017 ACC/AHA/HFSA Focused update of the 2013 ACCF/AHA HF guideline	Key points
	Non-invasive stress imaging (CMR, stress echocardiography, SPECT, PET) may be considered for the assessment of myocardial ischaemia and viability in patients with HF and CAD (considered suitable for coronary revascularization) before the decision on revascularization (class IIb, LOE B) CMR with LGE should be considered in patients with dilated cardiomyopathy to distinguish between ischaemic and non-ischaemic myocardial damage in case of equivocal clinical and other imaging data (taking account of cautions/contraindications to CMR) (class IIa, LOE C) Cardiac CT may be considered in patients with HF and low to intermediate pre-test probability of CAD or those with equivocal non-invasive stress tests in order to rule out coronary artery stenosis (class IIb, LOE C)	Non-invasive imaging to detect myocardial ischemia and viability is reasonable in patients presenting with de novo HF, who have known CAD and no angina, unless the patient is not eligible for revascularization of any kind (class IIa, LOE C) Magnetic resonance imaging is reasonable when assessing myocardial infiltrative processes or scar burden (class IIa, LOE B)	
Risk stratification	No specific recommendation	Measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF (class I, LOE A) Measurement of other clinically available tests such as biomarkers of myocardial injury or fibrosis may be considered for additive risk stratification in patients with chronic HF (class IIb, LOE B) Measurement of BNP or NT-proBNP and/or cardiac troponin is useful for establishing prognosis or disease severity in acutely decompensated HF (class I, LOE A) Measurement of other clinically available tests such as biomarkers of myocardial injury or fibrosis may be considered for additive risk stratification in patients with acutely decompensated HF (class IIb, LOE A)	NPs are established predictors of outcome in acute and chronic HF. Measurement of an hs-troponin, on at least one occasion, should be considered in outpatients with HFrEF Patients with hs-troponin T $\geq$18 ng/L have a greater risk of all-cause and cardiovascular mortality and hospitalization for cardiovascular causes regardless of LVEF, NT-proBNP, age, sex, renal function and ischaemic aetiology. sST2 levels further refine risk prediction of outpatients with HFrEF with 35 ng/mL as a useful cut-off. The clinical impact and therapeutic consequences of assessing risk, however, need to be investigated in clinical trials

Table 2 (Continued)

Setting	2016 ESC HF Guideline	2017 ACC/AHA/HFSA Focused update of the 2013 ACCF/AHA HF guideline	Key points
Guide to treatment and follow-up	The following diagnostic tests are recommended/should be considered for initial assessment of a patient with newly diagnosed HF to evaluate the patient's suitability for particular therapies, to detect reversible/treatable causes of HF and comorbidities interfering with HF: • […] • NPs (class IIa, LOE C)	BNP- or NT-proBNP-guided HF therapy can be useful to achieve optimal dosing of GDMT in select clinically euvolaemic patients followed in a well-structured HF disease management programme (class IIa, LOE B)	Circulating biomarkers play an important role as indicators for sonographic fluid status assessment and will improve the specificity of sonographic findings. We need well-designed randomized trials to test the concept of echo-guided decongestion with defined cut-offs for both echocardiographic measures and adjunctive circulating markers. Meanwhile, imaging markers and concurrent circulating biomarkers should be interpreted on a case-by-case basis. In chronic HFrEF, achieving concentrations of NT-proBNP <1000 ng/L is associated with reverse LV remodelling and a better prognosis. Sustained reduction in NT-proBNP below this level may allow a less intensive patient follow-up. HF recovery is revealed by longitudinal changes in imaging findings, most commonly from repeated echocardiography, and is accompanied by a reduction in NPs. Our current state of knowledge suggests that HF medications should be continued in patients with HFimpEF to prevent a new decline of cardiac function in a large proportion of this group. Rising NT-proBNP portends new deterioration of LV function in HFimpEF. Raised sST2 is associated with an increased risk of SCD and supports the decision to implant an ICD for primary prevention. The current discrepant state of evidence does not allow any clear recommendation about the possibility to guide CRT implantation based on circulating biomarkers or imaging findings related to myocardial fibrosis. Larger data sets with longer periods of follow-up assessing a wider range of candidate markers are required.

ACCF/AHA, American College of Cardiology Foundation/American Heart Association; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CMR, cardiac magnetic resonance; CRT, cardiac resynchronization therapy; CT, computed tomography; GDMT, guideline-directed medical therapy; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFSA, Heart Failure Society of America; hs, high-sensitivity; ICD, implantable cardioverter defibrillator; LGE, late gadolinium enhancement; LOE, level of evidence; LV, left ventricular; LVEF, left ventricular ejection fraction; NP, natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PET, positron emission tomography; SCD, sudden cardiac death; SPECT, single-photon emission computed tomography; sST2, soluble suppression of tumorigenesis-2; TTE, transthoracic echocardiogram.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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